Whipple Limbic Encephalitis

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Objective: To describe a relapse of Whipple disease revealed by isolated limbic encephalitis with no other signs of systemic involvement.

Design: Case report.

Setting: University Hospital of Strasbourg, Strasbourg, France.

Patient: A 41-year-old patient.

Main Outcome Measures: Cognitive functions and results of cerebrospinal fluid analysis and brain magnetic resonance imaging.

Results: A 41-year-old patient was hospitalized for headache associated with anterograde amnesia and temporal-spatial disorientation. Whipple disease with systemic manifestations was diagnosed 4 years previously and insufficiently treated. The neuropsychological evaluation showed impaired episodic memory and executive functions. Analysis of the cerebrospinal fluid showed increased lymphocytes and a positive T. whippelii polymerase chain reaction result. Cerebral magnetic resonance imaging revealed a typical pattern of limbic encephalitis with an intense signal in the amygdalae and hippocampi. The outcome under antibiotic treatment was marked by partial improvement of the cognitive disorders, disappearance of the positive T. whippelii polymerase chain reaction result in cerebrospinal fluid, and a clear decrease of inflammation on brain magnetic resonance imaging.

Conclusions: Whipple disease can present as limbic encephalitis. Few cases have been previously described in the literature. Such diagnosis is of importance because of the specific treatment.

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Whipple disease is a systemic bacterial infection due to T. whippelii. Its clinical manifestations generally include diarrhea, preceded in most cases by articular symptoms. Involvement of the central nervous system is possible, often being polymorphous but rarely isolated.

Limbic encephalitis (LE) is related to inflammation of the medial temporal lobe. Subacute amnesia is the main clinical symptom and can be associated with seizures and psychiatric symptoms such as depression or personality change. The main etiologies of LE are paraneoplastic, autoimmune, and viral, particularly herpetic LE. Excluding neurosyphilis, very few bacterial infections are responsible for LE.

We report 1 case of a relapse of Whipple disease revealed by isolated LE with no other signs of systemic involvement.

REPORT OF A CASE

A 41-year-old patient was hospitalized urgently for headache associated with major anterograde amnesia. These symptoms had developed progressively over several months. There was no fever, change in the general state of health, or diarrhea.

The patient was followed up for Whipple disease revealed 4 years earlier by migratory polyarthralgia, episodes of fever, and intermittent diarrhea. The diagnosis had been confirmed by a duodenal biopsy specimen that had shown inflammatory lesions containing macrophages with inclusions positive for periodic acid–Schiff. Results of the T. whippelii polymerase chain reaction (PCR) assay on the duodenal biopsy specimen were, however, negative. A course of antibiotics with a third-generation cephalosporin and cotrimoxazole had been prescribed for 15 months, but this treatment had not been maintained by the patient.

On hospital admission, the physical neurological examination was normal without meningeal syndrome. Conversely, a neuropsychological evaluation confirmed the presence of important disorders of the verbal and visual memory. On the Free and Cued Selective Reminding Test for verbal episodic memory, the patient had a score of 8 of 16 words for immediate recall (<5th percentile) and scores of 1 of 16 for free recall and 2 of 16 for total recall (<5th percentile). In the visual object recognition memory test...
of the cerebrospinal fluid (CSF) revealed 335 leukocytes/μL. The Wechsler Adult Intelligence Scale score likewise showed a retardation of the rate of processing information (25% of cases) and executive functions with an inhibition defect (error rate of 23 of 40 in the opposing order test). The Wechsler Adult Intelligence Scale score gave 94% and 98% correct answers at 3 months and 1 year. The disturbance of working memory remained unchanged. The episodic memory partially improved, with maximal scores of 11 words of 16 for immediate recall, 1 of 16 for free recall, and 4 of 16 for total recall on the Free and Cued Selective Reminding Test at 3 months and 4 of 16 for free recall and 11 of 16 for total recall at 1 year. On the DMS48 visual recognition test, the patient displayed great improvement and gave 94% and 98% correct answers at 3 months and 1 year, respectively. A new search of T whipplei by PCR in CSF was negative after 1 month of treatment. Follow-up brain magnetic resonance imaging performed after 3 months and 1 year showed a diminution of the internal temporal hypersignal (Figure, B). Conversely, an atrophy of the hippocampus appeared with persistence of a discrete uptake of contrast in the right temporal uncus and at the base of the third ventricle.

This relapse of Whipple disease has the particularity that it was revealed by LE. Involvement of the central nervous system is rare in Whipple disease but represents the most serious complication. It occurs during evolution of the disease in 10% to 20% of patients. In 2002, Gerard et al described in a literature review 122 patients with neuro-Whipple disease. Among these individuals, only 21 displayed isolated initial neurological involvement, while the majority had developed other extraneurological manifestations. Neurological symptoms appear especially in patients whose treatment has not included antibiotics able to cross the blood-brain barrier.

The neurological manifestations of Whipple disease are extremely diverse and poorly specific. Cognitive impairment is the most frequent and is detected in 71% of patients with neurological involvement. These disorders affect memory (25% of cases) and orientation (24% of cases) and can even lead to dementia (28% of cases). Oculomasticatory myorhythmia, always associated with vertical supranuclear gaze palsies, is detected in 8% to 20% of patients and has important diagnostic value as it is encountered only in Whipple disease.

Brain magnetic resonance imaging shows lesions in 53% of cases. These lesions consist of T2 or T2-
Results of CSF PCR analysis have been found to be negative in more than 30% of cases during neurological involvement of Whipple disease.\(^{12,13}\) Conversely, in some patients, results of the PCR assay remain positive in CSF despite antibiotic treatment and sometimes persist for years, without clinical relapse. This positivity can indicate either the persistence of an infectious agent insufficiently controlled by antibiotics or the persistence of residual DNA from dead organisms, which explains the controversial interest of PCR in therapeutic follow-up.\(^{13}\) In our patient, results of the PCR assay became negative after 1 month of antibiotic treatment.

Therapeutic recommendations are not based on any controlled trial. The strategy normally proposed is the administration of 160 mg of trimethoprim and 800 mg of sulfamethoxazole twice daily for 1 to 2 years, but relapse is possible.\(^{11}\) In neurological forms of the disease, a combination of hydroxychloroquine, cyclines, and sulfadiazine has been proposed,\(^{23}\) while according to Cooper et al.,\(^{26}\) in the case of neurological relapse while taking trimethoprim-sulfamethoxazole, cefixime can be quite efficacious. Hence, we opted in our case for triple antбиotherapy in association with hydroxychloroquine.

The prognosis in the event of involvement of the central nervous system remains somber, with a mortality of more than 25% at 4 years. One-quarter of the patients have severe sequelae.\(^{27}\) The evolution of our patient's disease was marked by partial preservation of the amnesia.

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